

Listing of Claims

This listing of claims replaces all prior versions and listings of claims in the application:

1. (Currently Amended) A method for constructing a model that ~~predicts~~
estimates sensitivity to a drug based on expression levels of genes, said method
comprising the steps of:

(a) obtaining sensitivity data for a collection of biological ~~specimen~~
specimens;

(b) obtaining gene expression data for the biological ~~specimen~~ specimens in
the collection; ~~and~~

(c) constructing a model by a partial least squares method type 1 using said
sensitivity data obtained in step (a) and at least a part of said gene expression data for
the biological ~~specimen~~ specimens obtained in step (b), wherein said model ~~can~~
~~predict~~ estimates the sensitivity of ~~[[the]]~~ a biological specimen to a specific drug;
and

(d) making said model available to estimate the sensitivity of the biological
specimen to the specific drug.

2. (Currently Amended) The method according to claim 1, wherein, in the step
(c), constructing the model is optimized by comprises constructing a model for each of
two or more sets of combinations of genes by the partial least squares method type 1 and
by selecting those models in which the number of genes is ~~small~~ smaller than the number

of genes in other models, and/or those models whose square of the predictive correlation coefficient (Q^2) value is ~~high~~ higher than the Q^2 values of other models, or those models in which the number of genes is smaller than the number of genes in other models and whose Q^2 value is higher than the Q^2 values of other models.

3. (Currently Amended) The method according to claim 2, wherein, in the step (c), constructing the model is ~~constructed by~~ comprises:

computing a parameter that represents a ~~degree of~~ contribution ~~for each of the~~ genes to estimations of the sensitivity of the biological specimen to the specific drug;
and

[[by]] selecting the genes that ~~have the~~ make relatively greater relative parameter contributions.

4. (Original) The method according to claim 3, wherein the parameter representing the degree of contribution is a modeling power value (Ψ).

5. (Currently Amended) The method according to claim 2, wherein, in the step (c), constructing the model is ~~constructed by~~ comprises generating different combinations of genes based on a genetic algorithm.

6. (Withdrawn) The method according to claim 1, wherein the sensitivity data comprises *in vitro* sensitivity data for a biological specimen.

7. (Withdrawn) The method according to claim 1, wherein the sensitivity data comprises animal-experimental sensitivity data for a biological specimen.

8. (Currently Amended) The method according to claim 1, wherein the sensitivity data comprises comprise clinical sensitivity data for a biological specimen.

9. (Original) The method according to claim 1, wherein the drug is selected from the group consisting of the following farnesyltransferase inhibitors:

a) 6-[Amino-(4-chloro-phenyl)-(3-methyl-3H-imidazol-4-yl)-methyl]-4-(3-chloro-phenyl)-1-methyl-1H-quinolin-2-one; hydrochloride (Code: R115777);

b) (R)-2,3,4,5-tetrahydro-1-(1H-imidazol-4-ylmethyl)-3-(phenylmethyl)-4-(2-thienylsulfonyl)-1H-1,4-benzodiazepine-7-carbonitrile (Code: BMS214662);

c) (+)-(R)-4-[2-[4-(3,10-Dibromo-8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl)piperidin-1-yl]-2-oxoethyl]piperidine-1-carboxamide (Code: SCH66336);

d) 4-[5-[4-(3-Chlorophenyl)-3-oxopiperazin-1-ylmethyl]imidazol-1-ylmethyl]benzonitrile (Code: L778123); and

e) 4-[hydroxy-(3-methyl-3H-imidazole-4-yl)-(5-nitro-7-phenyl-benzofuran-2-yl)-methyl]benzonitrile hydrochloride.

10. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following fluorinated pyrimidines:

a) [1-(3,4-Dihydroxy-5-methyl-tetrahydro-furan-2-yl)-5-fluoro-2-oxo-1,2-dihydro-pyrimidin-4-yl]-carbamic acid butyl ester (Code: capecitabine (Xeloda®);

b) 1-(3,4-Dihydroxy-5-methyl-tetrahydro-furan-2-yl)-5-fluoro-1H-pyrimidine-2,4-dione (Code: Furtulon);

- c) 5-Fluoro-1H-pyrimidine-2,4-dione (Code: 5-FU);
- d) 5-Fluoro-1-(tetrahydro-2-furanyl)-2,4(1H,3H)-pyrimidinedione (Code: Tegafur);
- e) a combination of Tegafur and 2,4(1H,3H)-pyrimidinedione (Code: UFT);
- f) a combination of Tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate (molar ratio of 1:0.4:1) (Code: S-1) ; and
- g) 5-Fluoro-N-hexyl-3,4-dihydro-2,4-dioxo-1(2H)-pyrimidinecarboxamide (Code: Carmofur).

11. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following taxanes:

- a) [2aR-[2a α ,4 β ,4a β ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]- β -(benzoylamino)- α -hydroxybenzenepropanoic acid 6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester (Code: Taxol);
- b) [2aR-[2a α ,4 β ,4a α ,6 β ,9 α (α R*, β S*),11 α ,12 α ,12a α ,12b α]]- β -[(1,1-dimethylethoxy)carbonyl]amino)- α -hydroxybenzenepropanoic acid 12b-(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,6,11-trihydroxy-4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester (Code: Taxotere);
- c) (2R,3S)-3-[[[(1,1-dimethylethoxy)carbonyl]amino]-2-hydroxy-5-methyl-4-hexenoic acid (3aS,4R,7R,8aS,9S,10aR,12aS,12bR,13S,13aS)-7,12a-bis(acetyloxy)-13-(benzyloxy)-3a,4,7,8,8a,9,10,10a,12,12a,12b,13-dodecahydro-9-hydroxy-5,8a,14,14-tetramethyl-2,8-dioxo-6,13a-methano-13aH-oxeto[2'',3''':5',6']benzo[1',2':4,5]cyclodeca[1,2-d]-1,3-dioxol-4-yl ester (Code: IDN 5109);

d) (2R,3S)- β -(benzoylamino)- α -hydroxybenzenepropanoic acid
(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6-(acetyloxy)-12-(benzoyloxy)-
2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-4,11-dihydroxy-12b-[(methoxycarbonyl)oxy]-
4a,8,13,13-tetramethyl-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester (Code:
BMS 188797); and

e) (2R,3S)- β -(benzoylamino)- α -hydroxybenzenepropanoic acid
(2aR,4S,4aS,6R,9S,11S,12S,12aR,12bS)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-
2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-4a,8,13,13-tetramethyl-4-
[(methylthio)methoxy]-5-oxo-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester (Code:
BMS 184476).

12. (Withdrawn) The method according to claim 1, wherein the drug is selected from the
group consisting of the following camptothecins:

a) 4(S)-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-
3,14(4H,12H)-dione (abbreviation: camptothecin);

b) [1,4'-bipiperidine]-1'-carboxylic acid, (4S)-4,11-diethyl-3,4,12,14-tetrahydro-4-
hydroxy-3,14-dioxo-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinolin-9-yl ester,
monohydrochloride (Code: CPT-11);

c) (4S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-
pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione monohydrochloride
(abbreviation: Topotecan);

d) (1S,9S)-1-amino-9-ethyl-5-fluoro-9-hydroxy-4-methyl-2,3,9,10,13,15-hexahydro-
1H,12H-benzo[de]pyrano[3',4':6,7]indolizino[1,2-b]quinoline-10,13-dione (Code: DX-8951f);

- e) 5(R)-ethyl-9,10-difluoro-1,4,5,13-tetrahydro-5-hydroxy-3H,15H-oxepino[3',4':6,7]indolizino[1,2-b]quinoline-3,15-dione (Code: BN-80915);
- f) (S)-10-amino-4-ethyl-4-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (Code: 9-aminocamptotecin); and
- g) 4(S)-ethyl-4-hydroxy-10-nitro-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione (Code: 9-nitrocamptothecin).

13. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following nucleoside analogue antitumor drugs:

- a) 2'-deoxy-2',2'-difluorocytidine (Code: DFDC);
- b) 2'-deoxy-2'-methylidenecytidine (Code: DMDC);
- c) (E)-2'-deoxy-2'-(fluoromethylene)cytidine (Code: FMDC);
- d) 1-(β -D-arabinofuranosyl)cytosine (Code: Ara-C);
- e) 4-amino-1-(2-deoxy- β -D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one (abbreviation: decitabine);
- f) 4-amino-1-[(2S,4S)-2-(hydroxymethyl)-1,3-dioxolan-4-yl]-2(1H)-pyrimidinone (abbreviation: troxacitabine);
- g) 2-fluoro-9-(5-O-phosphono- β -D-arabinofuranosyl)-9H-purin-6-amine (abbreviation: fludarabine); and
- h) 2-chloro-2'-deoxyadenosine (abbreviation: cladribine).

14. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following dolastatins:

a) N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[[[(1S)-2-phenyl-1-(2-thiazolyl)ethyl]amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-L-valinamide (abbreviation: dolastatin 10);

b) cyclo[N-methylalanyl-(2E,4E,10E)-15-hydroxy-7-methoxy-2-methyl-2,4,10-hexadecatrienoyl-L-valyl-N-methyl-L-phenylalanyl-N-methyl-L-valyl-N-methyl-L-valyl-L-prolyl-N2-methylasparaginy] (abbreviation: dolastatin 14);

c) (1S)-1-[(2S)-2,5-dihydro-3-methoxy-5-oxo-2-(phenylmethyl)-1H-pyrrol-1-yl]carbonyl]-2-methylpropyl ester N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-L-proline (abbreviation: dolastatin 15);

d) N,N-dimethyl-L-valyl-N-[(1S,2R)-2-methoxy-4-[(2S)-2-[(1R,2R)-1-methoxy-2-methyl-3-oxo-3-[(2-phenylethyl)amino]propyl]-1-pyrrolidinyl]-1-[(1S)-1-methylpropyl]-4-oxobutyl]-N-methyl-L-valinamide (Code: TZT 1027); and

e) N,N-dimethyl-L-valyl-L-valyl-N-methyl-L-valyl-L-prolyl-N-(phenylmethyl)-L-prolinamide (abbreviation: cemadotin).

15. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following anthracyclinesanthracyclines:

a) (8S,10S)-10-[(3-amino-2,3,6-trideoxy-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxynaphthacene-5,12-dione hydrochloride (abbreviation: adriamycin);

b) (8S,10S)-10-[(3-amino-2,3,6-trideoxy-L-arabino-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxynaphthacene-5,12-dione hydrochloride (abbreviation: epirubicin);

c) 8-acetyl-10-[(3-amino-2,3,6-trideoxy-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxynaphthacene-5,12-dione, hydrochloride (abbreviation: daunomycin); and

d) (7S,9S)-9-acetyl-7-[(3-amino-2,3,6-trideoxy-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,9,11-trihydroxynaphthacene-5,12-dione (abbreviation: idarubicin).

16. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following protein kinase inhibitors:

a) N-(3-chloro-4-fluorophenyl)-7-methoxy-6-[3-(4-morpholinyl)propoxy]-4-quinazolinamine (Code: ZD 1839);

b) N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine (Code: CP 358774);

c) N⁴-(3-bromophenyl)-N6-methylpyrido[3,4-d]pyrimidine-4,6-diamine (Code: PD 158780);

d) N-(3-chloro-4-((3-fluorobenzyl)oxy)phenyl)-6-(5-(((2-methylsulfonyl)ethyl)amino)methyl)-2-furyl)-4-quinazolinamine (Code: GW 2016);

e) 3-[(3,5-dimethyl-1H-pyrrol-2-yl)methylene]-1,3-dihydro-2H-indol-2-one (Code: SU5416);

f) (Z)-3-[2,4-dimethyl-5-(2-oxo-1,2-dihydro-indol-3-ylidenemethyl)-1H-pyrrol-3-yl]-propionic acid (Code: SU6668);

g) N-(4-chlorophenyl)-4-(pyridin-4-ylmethyl)phthalazin-1-amine (Code: PTK787);

h) (4-bromo-2-fluorophenyl)[6-methoxy-7-(1-methylpiperidin-4-ylmethoxy)quinazolin-4-yl]amine (Code: ZD6474);

- i) N^4 -(3-methyl-1H-indazol-6-yl)- N^2 -(3,4,5-trimethoxyphenyl)pyrimidine-2,4-diamine (Code: GW2286);
- j) 4-[(4-methyl-1-piperazinyl)methyl]-N-[4-methyl-3-[[4-(3-pyridinyl)-2-pyrimidinyl]amino]phenyl]benzamide (Code: STI-571);
- k) (9 α ,10 β ,11 β ,13 α)-N-(2,3,10,12,13-hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1H,9H-diindolo[1,2,3-gh:3',2',1'-1m]pyrrolo[3,4-j][1,7]benzodiazonin-11-yl)-N-methylbenzamide (Code: CGP41251);
- l) 2-[(2-chloro-4-iodophenyl)amino]-N-(cyclopropylmethoxy)-3,4-difluorobenzamide (Code: C11040); and
- m) N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea (Code: BAY439006).

17. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following platinum antitumor drugs:

- a) cis-diaminodichloroplatinum(II) (abbreviation: cisplatin);
 - b) diammine(1,1-cyclobutanedicarboxylato)platinum(II) (abbreviation: carboplatin);
- and
- c) hexaamminedichlorobis[μ -(1,6-hexanediamine- $\kappa N:\kappa N'$)]tri-,stereoisomer,tetranitrate platinum(4+) (Code: BBR3464).

18. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following epothilones:

a) 4,8-dihydroxy-5,5,7,9,13-pentamethyl-16-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-(4S,7R,8S,9S,13Z,16S)-oxacyclohexadec-13-ene-2,6-dione (abbreviation: epothilone D);

b) 7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-, (1S,3S,7S,10R,11S,12S,16R)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione-6-dione (abbreviation: epothilone); and

c) (1S,3S,7S,10R,11S,12S,16R)-7,11-dihydroxy-8,8,10,12,16-pentamethyl-3-[(1E)-1-methyl-2-(2-methyl-4-thiazolyl)ethenyl]-17-oxa-4-azabicyclo[14.1.0]heptadecane-5,9-dione (Code: BMS247550).

19. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following aromatase inhibitors:

a) $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-benzenediacetonitrile (Code: ZD1033);

b) (6-methyleneandrost-1,4-diene-3,17-dione (Code: FCE24304); and

c) 4,4'-(1H-1,2,4-triazol-1-ylmethylene)bis-benzonitrile (Code: CGS20267).

20. (Withdrawn) The method according to claim 1, wherein the drug is selected from the group consisting of the following hormone modulators:

a) 2-[4-[(1Z)-1,2-diphenyl-1-butenyl]phenoxy]-N,N-dimethylethanamine (abbreviation: tamoxifen);

- b) [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]methanone hydrochloride (Code: LY156758);
- c) 2-(4-methoxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]benzo[b]thiophene-6-ol hydrochloride (Code: LY353381);
- d) (+)-7-pivaloyloxy-3-(4'-pivaloyloxyphenyl)-4-methyl-2-(4''-(2'''-piperidinoethoxy)phenyl)-2H-benzopyran (Code: EM800);
- e) (E)-4-[1-[4-[2-(dimethylamino)ethoxy]phenyl]-2-[4-(1-methylethyl)phenyl]-1-butenyl]phenol dihydrogen phosphate(ester) (Code: TAT59);
- f) 17-(acetyloxy)-6-chloro-2-oxapregna-4,6-diene-3,20-dione (Code: TZP4238);
- g) (+,-)-N-[4-cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanamide (Code: ZD176334); and
- h) 6-D-leucine-9-(N-ethyl-L-prolinamide)-10-deglycinamide luteinizing hormone-releasing factor (pig) (abbreviation: leuprORElin).

21. (Original) The method according to claim 1, wherein the biological specimen is a cancer cell or a cancer cell line.

22. (Original) The method according to claim 1, wherein the sensitivity comprises an antitumor effect.

23. (Currently Amended) The method according to claim 1, wherein the gene expression data ~~comprises~~ comprise high-density nucleic acid array data.

24. (Withdrawn) A method for selecting genes that contribute to biological sensitivity to a high degree, said method comprising the step of selecting part or all of the combinations of genes in a model constructed by the method according to claim 1.

25. (Withdrawn- Currently Amended) A method for ~~predicting~~ estimating the sensitivity of a test specimen toward a particular stimulus, said method comprising the steps of:

(a) obtaining, for the test specimen, at least a part of a gene expression data from a model specimen constructed by the method according to claim 1; and

(b) correlating to the fact that the sensitivity is high, a high level of expression of a gene having a positive coefficient in the model and a low level of expression of a gene having a negative coefficient in the model, and correlating to the fact that the sensitivity is low, a low level of expression of a gene having a positive coefficient in the model and a high level of expression of a gene having a negative coefficient in the model.

26. (Withdrawn) The method according to claim 25, wherein:

step (a) comprises the step of obtaining the gene expression data in the model for the test specimen; and

step (b) comprises the step of computing the sensitivity by applying the expression data to the model.

27. (Withdrawn – Currently Amended) A computer device that ~~predicts~~ estimates the sensitivity of a test specimen toward a particular stimulus, said device comprising:

(a) a means for storing a parameter (model coefficient) representing the relationship between gene expression data and sensitivity value in a model constructed by the method according to claim 1;

(b) a means for inputting the gene expression data into the model;

(c) a means for storing the expression data;

(d) a means for predictively calculating the sensitivity value from the expression data and the parameter (model coefficient) based on the model;

(e) a means for storing the predictively calculated sensitivity value; and

(f) a means for outputting the predictively calculated sensitivity value or a result obtained from the sensitivity value.

28. (Withdrawn) A method for producing a high-density nucleic acid array, said method comprising the step of immobilizing or generating, on a support, nucleic acids comprising at least 15 nucleotides comprised in nucleotide sequences encoding respective genes selected by the method according to claim 24.

29. (Withdrawn) A method for producing a probe or a primer for quantitative or semi-quantitative PCR for respective genes selected by the method according to claim 24, said method comprising the step of synthesizing nucleic acids comprising at least 15 nucleotides comprised in nucleotide sequences encoding the respective genes.

30. (Withdrawn – Currently Amended) A kit comprising:

(a) a high-density nucleic acid array, or a probe or a primer for quantitative or semi-quantitative PCR, wherein said array, probe, or primer comprises nucleic acids comprising at least 15 nucleotides from nucleotide sequences encoding respective genes selected by the method according to claim 24; and

(b) a storage medium which records the sensitivity to drugs ~~predicted~~ estimated using the array, or the probe or the primer.

31. (Withdrawn) A method for selecting genes that contribute to biological sensitivity to a high degree, said method comprising the step of selecting part or all of the combinations of genes in a model constructed by the method according to claim 2.

32. (New) The method of claim 1, wherein the sensitivity data and the gene expression data comprise machine-readable data.

33. (New) The method of claim 1, wherein, in the step (d), making said model available comprises storing a description of the model on a data storage device or displaying the description of the model on a display screen.

34. (New) The method of claim 1, further comprising the step of (e) estimating the sensitivity of the biological specimen to the specific drug using the model.

35. (New) The method of claim 34, further comprising the step of (f) storing the estimate of the sensitivity of the biological specimen to the specific drug.

36. (New) The method of claim 1, wherein, in the step (a), obtaining the sensitivity data for a collection of biological specimens comprises obtaining sensitivity data for a collection of biological specimens, wherein the sensitivity data reflects the responsiveness of the biological specimens toward the specific drug.